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Polycyclic *N*-Hetero Compounds. XVIII.[1] Synthesis of the 11,13,15-Triazasteroidal Skeleton with an Oxygen Function at C-17

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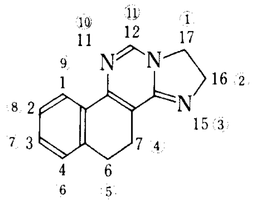
N-(5,6-Dihydro-4-benzo[*h*]quinazolinyl)amino acids (III and VII) were synthesized by condensation of 4-chloro-5,6-dihydrobenzo[*h*]quinazoline (II) with several amino acids and were cyclized to 4,5-dihydrobenz[*h*]imidazo[1,2-*c*]quinazoline derivatives, *i.e.*, 11,13,15-triazasteroidal compounds (IV, V, VI, VIII, and IX) using phosphoryl chloride or acetic anhydride. An oxygen function could be introduced at C-1 of 4,5-dihydrobenz[*h*]imidazo[1,2-*c*]quinazoline, *i.e.*, C-17 of the 11,13,15-triazasteroidal compounds.

Keywords——*N*-(4-benzo[*h*]quinazolinyl)amino acid; benz[*h*]imidazo[1,2-*c*]quinazoline; cyclization; acetylation; acetic anhydride; amino acid; phosphoryl chloride

There are no reports on the synthesis of compounds having a benz[*h*]imidazo[1,2-*c*]quinazoline ring, corresponding to the 11,13,15-triazasteroidal skeleton, except for our studies.[2] Interestingly, 1,2,4,5-tetrahydrobenz[*h*]imidazo[1,2-*c*]quinazoline (I), synthesized in our laboratory,[2] exhibited an antidepressive activity with moderate toxicity in mice.[3] However, this activity was not observed in 4-amino- and 4-hydroxy-5,6-dihydrobenzo[*h*]quinazolines which are similar to I in structure, and were the starting materials in the synthesis of I. Thus, we were interested in carrying out chemical modification of I in the hope that a more effective but non-toxic 11,13,15-triazasteroidal antidepressant could be found.

This paper deals with the synthesis of 16-substituted 11,13,15-triazasteroidal compounds with an oxygen function at C-17. Several *N*-(5,6-dihydro-4-benzo[*h*]quinazolinyl)amino acids (III and VII) were used as starting materials. As shown in Chart 1, *N*-(5,6-dihydro-4-benzo[*h*]quinazolinyl)glycine (III) was synthesized by condensation of 4-chloro-5,6-dihydrobenzo[*h*]quinazoline (II)[2b] with glycine in the presence of K_2CO_3.[4]

Cyclization of III with phosphoryl chloride gave a 17-oxo-11,13,15-triazasteroidal compound (IV) in low yield (8%) together with several colored products which immediately changed to other compounds. Infrared (IR) and proton nuclear magnetic resonance (NMR) spectra of IV showed a C=O band at $1686\,cm^{-1}$ and an $N-CH_2-CO$ signal at δ 4.52 ppm as a singlet, respectively. On the other hand, ring closure of III with phosphoryl chloride in dimethylformamide (DMF) afforded a 16-(*N*, *N*-dimethylaminomethylene)-17-oxo-11,13,15-triazasteroidal derivative (V) in 35% yield. The IR spectrum of V showed a C=O band at $1685\,cm^{-1}$. As compared with the NMR spectrum of IV, that of V indicated the disappearance of the two protons in $N-CH_2-CO$ and the appearance of $N(CH_3)_2$ at δ 3.22 (3H, s), 3.68 (3H, s) and $=C\underline{H}-N(CH_3)_2$ at δ 7.35 (1H, s) ppm. Although *E*–*Z* isomers might be formed in the case of compound V, the obtained compound showed a sharp singlet in its



I

IUPAC (in circle) and
steroidal (no mark) numberings

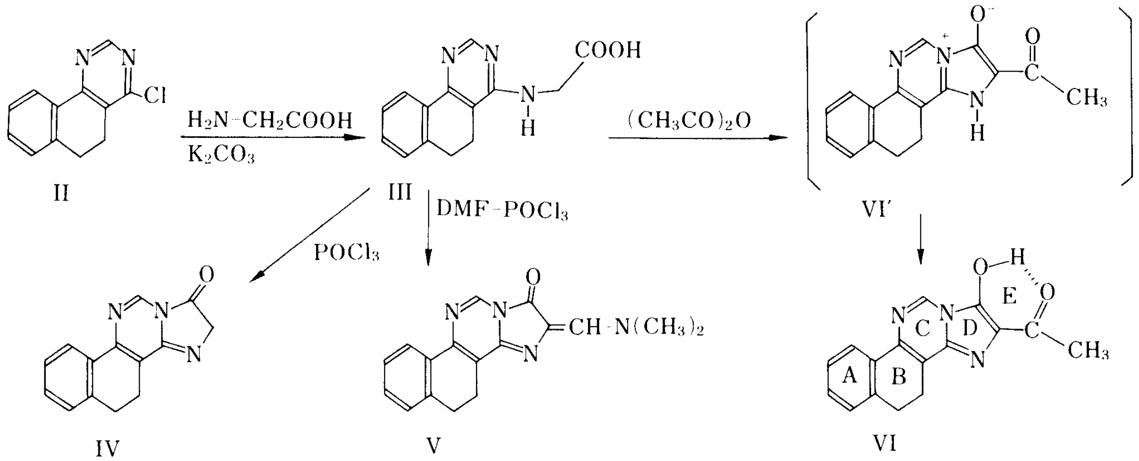


Chart 1

NMR as described above, indicating that only one isomer was isolated.

Treatment of III with excess acetic anhydride gave the 16-acetyl-17-hydroxy-11,13,15-triazasteroidal compound (VI) in satisfactory yield (72%). Compound VI readily dissolved in aqueous 5% NaOH solution, indicating that VI has an enolic hydroxyl group. However, attempts to further acetylate VI with acetic anhydride and pyridine were unsuccessful. These results suggest that a strong hydrogen bonding between the O–H and C=O groups in the D-ring probably contributes to the formation of the E-ring as shown in Chart 1. This suggestion is supported by the findings that the C=O and O–H bands appeared at 1640 and 2660 (broad) cm^{-1} in the IR spectrum and the signal of C-12 proton (pyrimidine ring proton) in the NMR spectrum was shifted to downfield (δ 10.24 ppm, s) by the anisotropic effect of the newly formed E-ring. In the conversion of III to VI by treatment with acetic anhydride, evaporation of excess acetic anhydride left a green-colored residue. This color changed to greenish-yellow when the residue was refluxed with dioxane or pyridine for recrystallization. Such a change in color was also observed during the development of this residue in thin-layer chromatography (TLC). Although the green product could not be isolated, it was supposed that a mesoionic green compound such as VI′ was initially formed and then converted immediately to the more stable VI during both recrystallization and TLC. Support for this assumption is given by the work of Maki *et al.*,[5] who reported the formation of mesoionic imidazo[2,1-*i*]purines by the treatment of 6-substituted purines with monochloroacetic anhydride.

As discussed above, the structures and yields of cyclization products of III, with no substituent at the α-position of the amino acid, depended upon the cyclization reagent used. This suggests that if *N*-(5,6-dihydro-4-benzo[*h*]quinazolinyl)valine (VIIb) is subjected to cyclization, the product with an isopropyl group at C-16 of the 11,13,15-triazasteroid and an oxygen function at C-17 should be formed. In fact, as shown in Chart 2, treatment of VIIb with phosphoryl chloride in DMF followed by basification afforded 17-hydroxy-16-isopropyl-11,13,15-triazasteroid (IX) in 10% yield. The IR spectrum of IX showed an O–H band at 3450 cm^{-1} instead of a C=O band at the amide carbonyl region, which indicated the presence of an enolic O–H group.

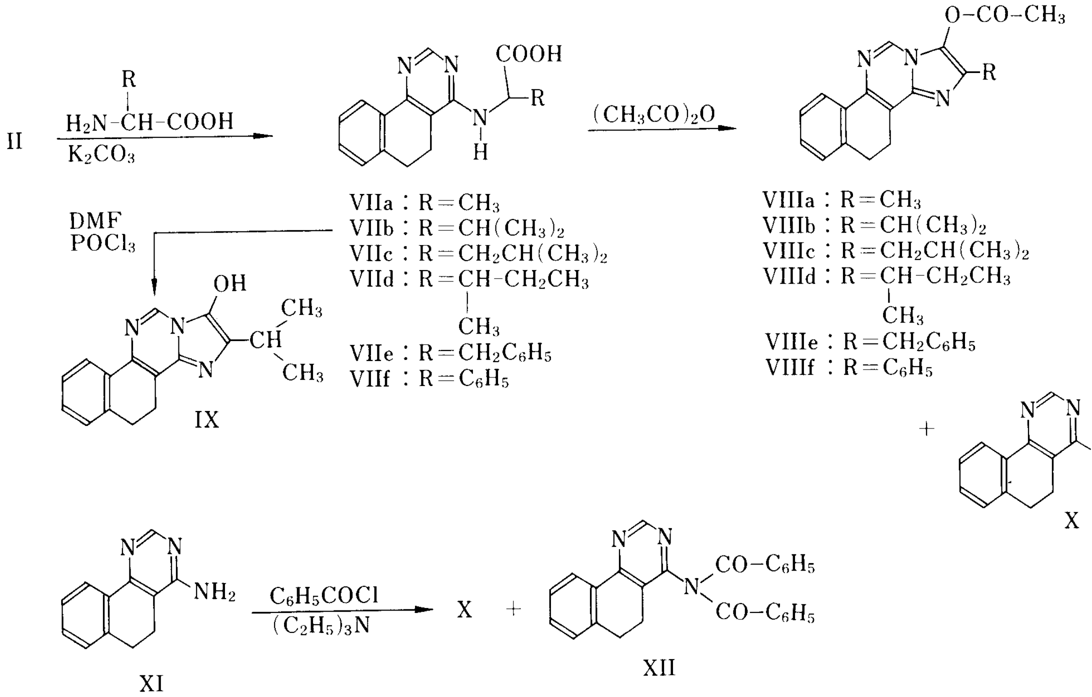


Chart 2

Treatment of VIIb with excess acetic anhydride gave 17-acetoxy-16-isopropyl-11,13,15-triazasteroid (VIIIb) in 79% yield. The NMR spectrum of VIIIb indicated the presence of an O-CO-CH_3 group at δ 2.47 (s) ppm, but the expected C=O band appeared at 1788 cm^{-1} in the IR spectrum. Although the latter value was higher than that for a usual C=O band in an enol acetate, we believe that this assignment is correct, because similar observations have been reported by Deady and Stanborough[6] for 3-acetoxy-6-methyl-2-phenylimidazo[2,1-*a*]-phthalazine (C=O; 1800 cm^{-1}) and by Ueda and Fox[7] for 1*H*-2-acetoxy-3-methyl-5-oxo-imidazo[1,2-*c*]pyrimidine (C=O; 1780 cm^{-1}). Since a satisfactory yield of a 11,13,15-tri-azasteroidal compound with an oxygen function at C-17 was obtained by using acetic anhydride as a cyclization reagent, this method was applied to the ring closure of *N*-(5,6-dihydro-4-benzo[*h*]quinazolinyl)amino acids (VII). Several DL-amino acids were incorporated at C-4 of 5,6-dihydrobenzo[*h*]quinazoline by a modification of the method of Vidal-Gomez *et al.*[4] in 55—95% yield. Cyclization of VII with acetic anhydride gave 16-substituted 17-acetoxy-11,13,15-triazasteroidal compounds, *i.e.*, 2-substituted 1-acetoxy-4,5-dihydro-benz[*h*]imidazo[1,2-*c*]quinazolines (VIII), in generally good yields. The data for these *N*-(5,6-dihydro-4-benzo[*h*]quinazolinyl)amino acids (VII) and 16-substituted 17-acetoxy-11,13,15-triazasteroidal compounds (VIII) are summarized in Tables I and II.

Ueda and Fox[7] reported that Dimroth-type rearrangement occurred when *N*-(1*H*-2-oxo-4-pyrimidinyl)-L-alanine was cyclized with acetic anhydride. However, the rearrangement did not occur in our case, because mild hydrolysis (refluxing with 5% acetic acid) of VIII gave the starting *N*-(5,6-dihydro-4-benzo[*h*]quinazolinyl)amino acids (VII), as checked by TLC.

In the cyclization reaction of VIIf to VIIIf, 4-benzamido-5,6-dihydrobenzo[*h*]quinazoline (X) was obtained along with VIIIf. The mechanism of its formation is not clear, but X was identical with the reaction product of 4-amino-5,6-dihydrobenzo[*h*]quinazoline (XI) and benzoyl chloride in the presence of triethylamine.

All the amino acid derivatives (III and VII) and 11,13,15-triazasteroidal derivatives (IV, V, VI, VIII, and IX) are new compounds. Their antidepressive activities will be reported elsewhere in the near future.

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Table I. *N*-(5,6-Dihydro-4-benzo[*h*]quinazolinyl)amino Acids (III and VIIa—f)

Compd. No.	React. time (h)	Yield (%)	mp (°C) (dec.)	Formula	Analysis (%) Calcd (Found) C	H	N
III	9	95$^{a)}$	130—133$^{d)}$	$C_{14}H_{13}N_3O_2$	65.87	5.13	16.46
					(65.69	5.38	16.30)
VIIa	10	91$^{a)}$	220—223$^{d)}$	$C_{15}H_{15}N_3O_2$	66.90	5.61	15.61
					(66.89	5.51	15.35)
VIIb	15	83$^{a)}$	179—182$^{d)}$	$C_{17}H_{19}N_3O_2$	68.66	6.44	14.13
					(68.44	6.25	13.90)
VIIc	20	55$^{b)}$	199—202$^{e)}$	$C_{18}H_{21}N_3O_2$	69.43	6.80	13.50
					(69.28	6.98	13.41)
VIId	35	80$^{b)}$	175—177$^{f)}$	$C_{18}H_{21}N_3O_2$	69.43	6.80	13.50
					(69.22	6.82	13.45)
VIIe	30	86$^{a)}$	213—216$^{f)}$	$C_{21}H_{19}N_3O_2$	73.02	5.55	12.17
					(72.90	5.49	12.04)
VIIf	30	72$^{c)}$	223—225$^{g)}$	$C_{20}H_{17}N_3O_2$	72.49	5.17	12.68
					(72.71	5.07	12.51)

a) Recrystallized from EtOH.
b) Recrystallized from dil. EtOH (70% EtOH was used in the case of VIIc).
c) Since VIIf did not dissolve in common organic solvents, it was dissolved in saturated $NaHCO_3$ solution, treated with charcoal, and acidified with acetic acid. The precipitated crystals were washed with H_2O.
d) Colorless prisms. *e*) Colorless granules.
f) Colorless needles. *g*) Powder.

Table II. 2-Substituted 1-Acetoxy-4,5-dihydrobenz[*h*]imidazo-[1,2-*c*]quinazolines (VIIIa—f)

Compd. No.	React. time (h)	Yield (%)	mp (°C) (dec.)	Formula	Analysis (%) Calcd (Found) C	H	N
VIIIa	0.3$^{a)}$	71$^{c)}$	171—173$^{e)}$	$C_{17}H_{15}N_3O_2$	69.61	5.15	14.33
					(69.44	5.14	14.58)
VIIIb	0.5$^{a)}$	79$^{d)}$	131—133$^{e)}$	$C_{19}H_{19}N_3O_2$	71.01	5.96	13.08
					(71.06	5.85	12.98)
VIIIc	0.5$^{a)}$	65$^{d)}$	103—105$^{e)}$	$C_{20}H_{21}N_3O_2$	71.62	6.31	12.53
					(71.44	6.24	12.41)
VIIId	5$^{b)}$	61$^{d)}$	103—105$^{e)}$	$C_{20}H_{21}N_3O_2$	71.62	6.31	12.53
					(71.52	6.27	12.48)
VIIIe	3$^{b)}$	72$^{c)}$	152—154$^{f)}$	$C_{23}H_{19}N_3O_2$	74.78	5.18	11.38
					(75.01	5.16	11.30)
VIIIf	3$^{b)}$	43$^{c)}$	169—171$^{g)}$	$C_{22}H_{17}N_3O_2$	74.35	4.82	11.84
					(74.24	4.75	12.02)

a) Heated at 100 °C. *b*) Stirred at room temperature.
c) Recrystallized from cyclohexane–benzene. *d*) Recrystallized from *n*-hexane.
e) Yellowish needles. *f*) Orange needles. *g*) Brown needles.

Experimental

Melting points were recorded on a Yanagimoto micro melting point apparatus and are uncorrected. Analyses were performed on a Yanagimoto MT-2 CHN Corder elemental analyzer. IR spectra were obtained with a Nihon Bunko A-102 spectrometer for KBr disks. NMR spectra were measured with a Hitachi R22-FTS instrument

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(90 MHz) with tetramethylsilane as an internal standard (δ value). Mass spectra (MS) were taken with a Shimadzu LKB-9000 spectrometer. Ultraviolet (UV) spectra were taken on a Hitachi ESP-2 spectrophotometer. DL-Amino acids were used in these experiments. IUPAC numbering is used for all compounds in the experimental section (not steroidal numbering).

General Procedure for the Synthesis of *N*-(5,6-Dihydro-4-benzo[*h*]quinazolinyl) Amino Acids except for VIIc (III and VII)——A mixture of 5 mmol of 4-chloro-5,6-dihydrobenzo[*h*]quinazoline (II), 20 mmol (10 mmol in the case of VIId—f) of amino acid, and 10 mmol (5 mmol in the case of VIId—f) of K_2CO_3 in 30 ml of HO–CH_2CH_2–OCH_3–H_2O (1 : 1) was refluxed for an appropriate time until the disappearance of II (TLC check). The resulting solution was evaporated to dryness under a vacuum and then about 20 ml of H_2O was added to give a clear solution. Acetic acid was gradually added to the solution until colorless crystals precipitated. The deposited crystals were filtered off, washed with a small amount of H_2O, and recrystallized from an appropriate solvent.

In some cases, a small amount of 4-hydroxy-5,6-dihydrobenzo[*h*]quinazoline,[2b)] which dissolved in aq. K_2CO_3, was formed (TLC check) when prolonged heating was needed. In such cases, the above precipitated crystals (*N*-(5,6-dihydro-4-benzo[*h*]quinazolinyl)amino acid and 4-hydroxy-5,6-dihydrobenzo[*h*]quinazoline) were dissolved in excess $NaHCO_3$ solution and the solution, which included the insoluble hydroxy derivative, was filtered. The mother liquor was acidified with acetic acid and the deposited crystals were recrystallized. The reaction times, yields, melting points, and analyses of III and VIIa—f are listed in Table I.

N-(5,6-Dihydro-4-benzo[*h*]quinazolinyl)glycine (III): NMR ($(CD_3)_2SO$): 2.75 (4H, m, CH_2CH_2), 3.99 (2H, d, $J=6$ Hz, CH_2–N, changed to singlet with D_2O), 7.26 and 8.08 (4H, 1H, NH, aromatic H, 4H became 3H with D_2O), 8.35 (1H, s, pyrimidine H). MS *m/e*: 255 (M^+), 254 (M^+-H), 237 (M^+-H_2O), 211 (M^+-CO_2), 210 (M^+-COOH, base peak). IR $\nu_{\max}^{\mathrm{KBr}}$ cm^{-1}: 3390, 3230, 2500 (br), 1660 (sh), 1632, 1585.

N-(5,6-Dihydro-4-benzo[*h*]quinazolinyl)alanine (VIIa): NMR ($(CD_3)_2SO$): 1.46 (3H, d, $J=7$ Hz, CH_3), 2.76 (4H, m, CH_2CH_2), 4.59 (1H, m, N–CH–CO), 6.99 (1H, d, $J=7$ Hz, NH, disappeared with D_2O), 7.34 and 8.18 (3H, 1H, m, aromatic H), 8.45 (1H, s, pyrimidine H). MS *m/e*: 269 (M^+), 268 (M^+-H), 251 (M^+-H_2O), 225 (M^+-CO_2), 224 (M^+-COOH, base peak). IR $\nu_{\max}^{\mathrm{KBr}}$ cm^{-1}: 3380, 2400 (br, w), 1727, 1620, 1583.

N-(5,6-Dihydro-4-benzo[*h*]quinazolinyl)valine (VIIb): NMR ($(CD_3)_2SO$): 0.95, 1.22 (3H, 3H, d, $J=6$ Hz, $2\times CH_3$), 2.35 (1H, m, $C\underline{H}(CH_3)_2$), 2.88 (4H, m, CH_2CH_2), 4.47 (1H, t, $J=8$ Hz, N–CH–CO, triplet became doublet with D_2O), 6.62 (1H, d, $J=8$ Hz, NH, disappeared with D_2O), 7.38 and 8.18 (3H, 1H, m, aromatic H), 8.46 (1H, s, pyrimidine H), 10.39 (1H, br, COOH, disappeared with D_2O). MS *m/e*: 297 (M^+), 296 (M^+-H), 279 (M^+-H_2O), 253 (M^+-CO_2), 252 (M^+-COOH), 236 (M^+-H_2O, $-CH(CH_3)_2$, base peak). IR $\nu_{\max}^{\mathrm{KBr}}$ cm^{-1}: 3360 (br), 2500 (br, w), 1710, 1630, 1583.

N-(5,6-Dihydro-4-benzo[*h*]quinazolinyl)leucine (VIIc): The reaction was carried out by the general method. However, VIIc and excess leucine were deposited as a mixture when acetic acid was added to the H_2O solution of the resulting residue. Separation of VIIc and leucine was achieved as follows. The mixed crystals were washed with a large quantity of hot water. The hot EtOH–MeOH-soluble part of the residue was collected, because a large amount of leucine remained in the insoluble part. The EtOH–MeOH solution was evaporated and the residue was recrystallized from 70% EtOH. The first crop was leucine. The mother liquor was concentrated until the appearance of crystals, which were almost pure VIIc. This VIIc was recrystallized from 80% EtOH. NMR ($(CD_3)_2SO$): 0.99, 1.02 (3H, 3H, d, $J=6.5$ Hz, $2\times CH_3$), 1.74 (3H, m, $C\underline{H}_2C\underline{H}(CH_3)_2$), 2.84 (4H, m, CH_2CH_2), 4.63 (1H, m, N–CH–CO), 6.96 (1H, d, $J=8$ Hz, NH, disappeared with D_2O), 7.36 and 8.20 (3H, 1H, m, aromatic H), 8.46 (1H, s, pyrimidine H). MS *m/e*: 311 (M^+), 310 (M^+-H), 293 (M^+-H_2O), 267 (M^+-CO_2), 266 (M^+-COOH), 250 (M^+-H_2O, $-CH(CH_3)_2$, base peak), 236 (M^+-H_2O, $-CH_2CH(CH_3)_2$). IR $\nu_{\max}^{\mathrm{KBr}}$ cm^{-1}: 3400 (br), 2490 (br, w), 1705, 1635, 1585.

N-(5,6-Dihydro-4-benzo[*h*]quinazolinyl)isoluecine (VIId): NMR ($(CD_3)_2SO$): 0.88 (3H, t, $J=7.5$ Hz, CH_3), 1.08 (3H, d, $J=6.5$ Hz, CH_3), 1.40 (2H, m, CH_2), 2.01 (1H, m, $C\underline{H}(CH_3)C_2H_5$), 2.86 (4H, m, CH_2CH_2), 4.52 (1H, t, $J=7.5$ Hz, N–CH–CO, changed to doublet with D_2O), 6.58 (1H, d, $J=7.5$ Hz, NH, disappeared with D_2O), 7.34 and 8.13 (3H, 1H, m, aromatic H), 8.45 (1H, s, pyrimidine H), 12.10 (1H, br, COOH, disappeared with D_2O). MS *m/e*: 311 (M^+), 310 (M^+-H), 293 (M^+-H_2O), 267 (M^+-CO_2), 266 (M^+-COOH), 236 (M^+-H_2O, $-CH(CH_3)C_2H_5$, base peak). IR $\nu_{\max}^{\mathrm{KBr}}$ cm^{-1}: 3420, 2450 (br), 1710, 1630 (sh), 1615 (sh), 1580.

N-(5,6-Dihydro-4-benzo[*h*]quinazolinyl)phenylalanine (VIIe): NMR ($(CD_3)_2SO$): 2.83 (4H, m, CH_2CH_2), 3.21 (2H, d, $J=7.5$ Hz, CH_2), 4.82 (1H, m, N–CH–CO, changed to triplet with D_2O), 7.02 (1H, d, $J=7.5$ Hz, NH, disappeared with D_2O), 7.30 and 8.13 (8H, 1H, m, aromatic and phenyl H), 8.42 (1H, s, pyrimidine H). MS *m/e*: 345 (M^+), 344 (M^+-H), 327 (M^+-H_2O), 300 (M^+-COOH), 236 (M^+-H_2O, $-CH_2C_6H_5$, base peak). IR $\nu_{\max}^{\mathrm{KBr}}$ cm^{-1}: 3390, 2450 (br), 1702, 1635 (sh), 1615 (sh), 1583.

N-(5,6-Dihydro-4-benzo[*h*]quinazolinyl)phenylglycine (VIIf): NMR ($(CD_3)_2SO$): 2.88 (4H, m, CH_2CH_2), 5.75 (1H, d, $J=7$ Hz, N–CH–CO, changed to singlet with D_2O), 7.16 (1H, d, $J=7$ Hz, NH, disappeared with D_2O), 7.40 and 8.15 (8H, 1H, m, aromatic and phenyl H), 8.49 (1H, s, pyrimidine H). MS *m/e*: 331 (M^+), 330 (M^+-H), 313 (M^+-H_2O, base peak), 287 (M^+-CO_2), 286 (M^+-COOH), 236 (M^+-H_2O, $-C_6H_5$). IR $\nu_{\max}^{\mathrm{KBr}}$ cm^{-1}: 3320, 2500 (br), 1702, 1625, 1578.

Reaction of III with $POCl_3$——A mixture of 255 mg (1 mmol) of III and 5 ml of $POCl_3$ was refluxed for 3 h. The crystals (III) dissolved gradually during 0.5 h. After evaporation of excess $POCl_3$, the residue was dissolved in H_2O

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and then the solution was basified with K_2CO_3 and extracted with $CHCl_3$ (the color changed in this step). The $CHCl_3$ layer was washed with H_2O, dried over Na_2SO_4, and evaporated to dryness. After treatment of the residue in EtOH solution with charcoal, the resulting residue was repeatedly recrystallized from benzene to give 19 mg (8%) of 1-oxo-1,2,4,5-tetrahydrobenz[*h*]imidazo[1,2-*c*]quinazoline (IV) as a pale brown powder, mp 185—188 °C. *Anal.* Calcd for $C_{14}H_{11}N_3O$: C, 70.87; H, 4.67; N, 17.71. Found: C, 70.65; H, 4.79; N, 17.53. NMR ($CDCl_3$): 2.97 (4H, s, CH_2CH_2), 4.52 (2H, s, N–CH_2–CO), 7.32 and 8.17 (3H, 1H, m, aromatic H), 8.35 (1H, s, pyrimidine H). MS *m/e*: 237 (M^+), UV $\lambda_{\max}^{\text{ethanol}}$ nm (log ε): 212 (4.47), 246 (4.41), 257 (4.43), 289 (4.33), 359 (4.02).

Reaction of III with $POCl_3$ in DMF——A solution of 255 mg (1 mmol) of III in 10 ml of dry DMF was treated with 383 mg (2.5 mmol) of $POCl_3$, and the mixture was allowed to stand for 15 min at room temperature. After the addition of 50 ml of ice water to the reaction mixture, the resulting solution was basified with $NaHCO_3$ and extracted with CH_2Cl_2. The CH_2Cl_2 layer was worked up as usual and evaporated to dryness under a vacuum. The residue was chromatographed on silica gel with benzene. After the elution with benzene, the Et_2O eluate was collected and recrystallized from benzene to give 102 mg (35%) of 2-(*N*,*N*-dimethylaminomethylene)-1-oxo-1,2,4,5-tetrahydrobenz[*h*]imidazo[1,2-*c*]quinazoline (V) as pale brown needles, mp 269—271 °C. *Anal.* Calcd for $C_{17}H_{16}N_4O$: C, 69.84; H, 5.52; N, 19.17. Found: C, 69.61; H, 5.67; N, 19.02. NMR ($CDCl_3$): 2.90 (4H, s, CH_2CH_2), 3.22 and 3.68 (each 3H, s, $N(CH_3)_2$), 7.20 and 8.04 (3H, 1H, m, aromatic H), 7.35 (1H, s, CH=N), 8.51 (1H, s, pyrimidine H). MS *m/e*: 292 (M^+). UV $\lambda_{\max}^{\text{ethanol}}$ nm (log ε): 213 (3.03), 279 (4.02), 424 (3.82), 448.5 (3.91), 475 (3.74).

Reaction of III with $(CH_3CO)_2O$——A mixture of 255 mg (1 mmol) of III and 1 ml of $(CH_3CO)_2O$ was heated at 100 °C for 1.5 h. After evaporation of the excess $(CH_3CO)_2O$, the greenish residue was triturated with benzene to give a greenish-yellow powder. The powder was recrystallized from pyridine to give 201 mg (72%) of 2-acetyl-1-hydroxy-4,5-dihydrobenz[*h*]imidazo[1,2-*c*]quinazoline (VI) as yellow needles, mp 272—273 °C. *Anal.* Calcd for $C_{16}H_{13}N_3O_2$: C, 68.80; H, 4.69; N, 15.05. Found: C, 68.79; H, 4.66; N, 15.19. NMR ($(CD_3)_2SO$): 2.41 (3H, s, CH_3), 3.01 (4H, s, CH_2CH_2), 7.36 and 8.16 (3H, 1H, m, aromatic H), 10.24 (1H, s, pyrimidine H). MS *m/e*: 279 (M^+). UV $\lambda_{\max}^{\text{ethanol}}$ nm (log ε): 243 (4.33), 269 (4.23), 280 (4.11), 366 (4.28), 377 (4.30).

Reaction of *N*-(5,6-Dihydro-4-benzo[*h*]quinazolinyl)valine (VIIb) with $POCl_3$ in DMF——A solution of 148 mg (0.5 mmol) of VIIb in 2 ml of DMF was treated with 0.1 ml of $POCl_3$ and the mixture was stirred for 1 h at room temperature. After addition of H_2O to the resulting solution, the deposited reddish-brown amorphous material was filtered off (*ca.* 60 mg); it showed many spots on TLC. The mother liquor was evaporated to dryness under a vacuum. The residue was triturated with H_2O and the insoluble brown powder was filtered off (*ca.* 30 mg); it showed many spots on TLC. The mother liquor was basified with $NaHCO_3$ and allowed to stand in a refrigerator for 2 d. The deposited pale yellow crystals were collected and washed with H_2O, then recrystallized from benzene–CH_2Cl_2 to give 14 mg (10%) of 1-hydroxy-2-isopropyl-4,5-dihydrobenz[*h*]imidazo[1,2-*c*]quinazoline (IX) as pale yellow needles, mp 168—170 °C. *Anal.* Calcd for $C_{17}H_{17}N_3O$: C, 73.09; H, 6.13; N, 15.04. Found: C, 72.88; H, 6.01; N, 14.90. NMR (CD_3OD): 0.97, 1.17 (3H, 3H, d, J=7 Hz, 2×CH_3), 2.60 (1H, m, $\underline{C}\underline{H}(CH_3)_2$), 3.00 (4H, m, CH_2CH_2), 7.44 and 8.33 (3H, 1H, m, aromatic H), 8.71 (1H, s, pyrimidine H). MS *m/e*: 279 (M^+), 264 ($M^+ - CH_3$, base peak). IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 3450 (O–H).

General Procedure for the Synthesis of 2-Substituted 1-Acetoxy-4,5-dihydrobenz[*h*]imidazo[1,2-*c*]quinazolines (VIII)——Method A (VIIIa—c): A mixture of 1 mmol of dry powdered VII and 1 ml of $(CH_3CO)_2O$ was heated at 100 °C for an appropriate time. After evaporation of the excess $(CH_3CO)_2O$, xylene was added to the residue and evaporated to dryness (twice) to remove residual $(CH_3CO)_2O$. The residue was recrystallized from an appropriate solvent.

Method B (VIIId—e): $(CH_3CO)_2O$ (2.5 mmol) was added to a solution of 1 mmol of VII in 5 ml of pyridine, and the mixture was stirred at room temperature for an appropriate time. After evaporation of the pyridine and $(CH_3CO)_2O$, xylene was added to the residue and evaporated to dryness (twice) to remove residual pyridine and $(CH_3CO)_2O$. The resulting residue was recrystallized from an appropriate solvent. The reaction times, yields, melting poins, and analyses of VIIIa—f are listed in Table II.

1-Acetoxy-2-methyl-4,5-dihydrobenz[*h*]imidazo[1,2-*c*]quinazoline (VIIIa): NMR ($CDCl_3$): 2.37 and 2.47 (each 3H, each s, CH_3, $COCH_3$), 3.17 (4H, m, CH_2CH_2), 7.28 and 8.19 (3H, 1H, m, aromatic H), 8.53 (1H, s, pyrimidine H). MS *m/e*: 293 (M^+), 251 ($M^+ - CH_2=C=O$, base peak). IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 1785, 1195 (O–CO–CH_3). UV $\lambda_{\max}^{\text{ethanol}}$ nm (log ε): 232 (4.39), 268 (3.87), 290 (4.10), 315 (4.34), 348 (4.20).

1-Acetoxy-2-isopropyl-4,5-dihydrobenz[*h*]imidazo[1,2-*c*]quinazoline (VIIIb): NMR ($CDCl_3$): 1.38 (6H, d, J=7 Hz, 2×CH_3), 2.47 (3H, s, $COCH_3$), 3.17 (5H, m, $\underline{C}\underline{H}(CH_3)_2$ and CH_2CH_2), 7.28 and 8.20 (3H, 1H, m, aromatic H), 8.50 (1H, s, pyrimidine H). MS *m/e*: 321 (M^+), 279 ($M^+ - CH_2=C=O$, base peak), 264 ($M^+ - CH_2=C=O$, $-CH_3$), 236 ($M^+ - CH_2=C=O$, $-CH(CH_3)_2$). IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 1788, 1178 (O–CO–CH_3). UV $\lambda_{\max}^{CH_2Cl_2}$ nm (log ε): 243 (4.37), 280 (4.01), 290 (4.11), 317 (4.29), 340 (4.10).

1-Acetoxy-2-isobutyl-4,5-dihydrobenz[*h*]imidazo[1,2-*c*]quinazoline (VIIIc): NMR ($CDCl_3$): 0.96 (6H, d, J=6 Hz, 2×CH_3), 2.17 (1H, m, $\underline{C}\underline{H}(CH_3)_2$), 2.47 (3H, s, $COCH_3$), 2.58 (2H, d, J=7 Hz, $\underline{C}\underline{H}_2CH$), 3.16 (4H, m, CH_2CH_2), 7.28 and 8.22 (3H, 1H, m, aromatic H), 8.52 (1H, s, pyrimidine H). MS *m/e*: 335 (M^+), 293 ($M^+ - CH_2=C=O$), 250 ($M^+ - CH_2=C=O$, $-CH(CH_3)_2$, base peak). IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 1770, 1181 (O–CO–CH_3). UV $\lambda_{\max}^{CH_2Cl_2}$ nm (log ε): 242 (4.49), 256 (4.40), 288 (4.32), 306 (4.40), 315 (4.39), 340 (4.02).

1-Acetoxy-2-*sec*-butyl-4,5-dihydrobenz[*h*]imidazo[1,2-*c*]quinazoline (VIIId): NMR ($CDCl_3$): 0.89 (3H, t, $J=7\,Hz$, $CH_2C\underline{H}_3$), 1.36 (3H, d, $J=7.5\,Hz$, $CHC\underline{H}_3$), 1.73 (2H, m, $C\underline{H}_2CH_3$), 2.46 (3H, s, $COCH_3$), 2.87 (1H, m, $C\underline{H}CH_3$), 3.17 (4H, m, CH_2CH_2), 7.26 and 8.20 (3H, 1H, m, aromatic H), 8.51 (1H, s, pyrimidine H). MS *m/e*: 335 (M^+), 293 ($M^+-CH_2=C=O$, base peak). IR $\nu_{\max}^{KBr}\,cm^{-1}$: 1795, 1170 (O–CO–$CH_3$). UV $\lambda_{\max}^{\text{ethanol}}$ nm ($\log\varepsilon$): 232 (4.60), 242 (4.60), 279 (4.13), 290 (4.33), 315 (4.55), 340 (4.40).

1-Acetoxy-2-benzyl-4,5-dihydrobenz[*h*]imidazo[1,2-*c*]quinazoline (VIIIe): NMR ($CDCl_3$): 2.15 (3H, s, $COCH_3$), 3.16 (4H, m, CH_2CH_2), 4.15 (2H, s, CH_2), 7.30 and 8.20 (8H, 1H, br s, m, aromatic H), 8.50 (1H, s, pyrimidine H). MS *m/e*: 369 (M^+, base peak), 327 ($M^+-CH_2=C=O$). IR $\nu_{\max}^{KBr}\,cm^{-1}$: 1781, 1175 (O–CO–$CH_3$). UV $\lambda_{\max}^{\text{ethanol}}$ nm ($\log\varepsilon$): 240 (4.32), 250 (4.33), 290 (4.04), 316 (4.27), 338 (4.14).

Reaction of *N*-(5,6-Dihydro-4-benzo[*h*]quinazolinyl)phenylglycine (VIIf) with $(CH_3CO)_2O$——$(CH_3CO)_2O$ (0.77 g, 7.55 mmol) was added to a solution of 500 mg (1.51 mmol) of VIIf in 5 ml of pyridine, and the mixture was stirred at room temperature. After evaporation of the solvent, 5 ml of xylene was added to the residue and evaporated (twice) again. The residue was recrystallized from benzene to give 231 mg (43%) of 1-acetoxy-2-phenyl-5,6-dihydrobenz[*h*]imidazo[1,2-*c*]quinazoline (VIIIf). NMR ($CDCl_3$): 2.53 (3H, s, $COCH_3$), 3.21 (4H, m, CH_2CH_2), 7.42, 8.00, and 8.22 (6H, 2H, 1H, each m, aromatic H), 8.55 (1H, s, pyrimidine H). MS *m/e*: 355 (M^+), 313 ($M^+-CH_2=C=O$), 284 ($M^+-CH_2=C=O$, –CHO, base peak). IR $\nu_{\max}^{KBr}\,cm^{-1}$: 1784, 1169 (O–CO–$CH_3$). UV $\lambda_{\max}^{\text{ethnaol}}$ nm ($\log\varepsilon$): 204 (4.32), 253 (4.36), 307 (4.01), 318 (4.07), 350 (3.96), 370 (3.74). After evaporation of the mother liquor of VIIIf, the residue was recrystallized from benzene–cyclohexane to give 91 mg (20%) of 4-benzamido-5,6-dihydrobenzo[*h*]quinazoline (X) as colorless fine needles, mp 223—225 °C. *Anal.* Calcd for $C_{19}H_{15}N_3O$: C, 75.73; H, 5.02; N, 13.95. Found: C, 75.53; H, 4.92; N, 13.67. NMR ($CDCl_3$): 2.93 (4H, s, CH_2CH_2), 7.44, 7.99, and 8.34 (6H, 2H, 1H, each m, aromatic H), 8.58 (1H, br, NH, disappeared with D_2O), 8.89 (1H, s, pyrimidine H). MS *m/e*: 301 (M^+), 224 ($M^+-C_6H_5$), 196 ($M^+-COC_6H_5$). IR $\nu_{\max}^{KBr}\,cm^{-1}$: 3190 (N–H), 1650 (C=O).

Reaction of 4-Amino-5,6-dihydrobenzo[*h*]quinazoline (XI) with Benzoyl Chloride——A mixture of 197 mg (1 mmol) of XI, 183 mg (1.3 mmol) of benzoyl chloride, and 152 mg (1.5 mmol) of Et_3N in 5 ml of dioxane was heated at 80 °C for 4 h with strring. After addition of 2 volumes of H_2O, the deposited crystals were filtered off. Since the crystals showed two spots on TLC, separation was carried out by preparative TLC (Wakogel B-5FM, 20 cm × 20 cm × 1 mm, $CHCl_3 : (CH_3)_2CO = 1 : 1$). The fraction with *Rf ca.* 0.5—0.6 was collected and recrystallized from benzene–cyclohexane to give 118 mg (39%) of X, which was identical with the above product on the basis of mixed mp, TLC, and instrumental data.

.The fraction of *Rf ca.* 0.75—0.85 was collected and recrystallized from benzene–cyclohexane to give 85 mg (21%) of 4-(dibenzoylamino)-5,6-dihydrobenzo[*h*]quinazoline (XII) as colorless feathers, mp 228—230 °C. *Anal.* Calcd for $C_{26}H_{19}N_3O_2$: C, 77.02, H, 4.72; N, 10.37. Found: C, 77.27; H, 4.89; N, 10.47. NMR ($CDCl_3$): 2.93 (4H, s, CH_2CH_2), 7.35, 8.37, and 8.82 (9H, 4H, 1H, each m, aromatic H), 8.89 (1H, s, pyrimidine H). MS *m/e*: 405 (M^+), 377 (M^+-CO), 300 ($M^+-COC_6H_5$, base peak), 195 ($M^+-2\times COC_6H_5$). IR $\nu_{\max}^{KBr}\,cm^{-1}$: 1695 (C=O), 1705 (sh).

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